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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/920,517	CLARKE ET AL.	
	Examin r	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,18-35,38-183,185-188,194 and 196-198* is/are pending in the application.

4a) Of the above claim(s) *31 and 41-183* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,18-30,32-35,38-40,185-188,194 and 196-198* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed on May 29, 2003 has been entered as paper#13. Claims 15-17, 36, 37, 184, 189-193, and 195 have been canceled. Claims 31 and 41-183 are withdrawn from consideration as they are drawn to non-elected inventions. Claims 1, 12, 18, 23, 32, 39, 187, and 198 have been amended. Currently, claims 1-14, 18-30, 32-35, 38-40, 185-188, 194, 196-198 are under examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in paper #13 would be addressed to the extent that they apply to current rejection.

WRITTEN DESCRIPTION REQUIREMENT

Claims 32-35, 38-40, 188, and 198 stand rejected under 35 U.S.C. 112, 1st paragraph, and the rejection now applies to claims 1-14, 18-30, 185-187, 194, 196, and 197, for reasons of record and following.

The amended claims 1-14, 18-30, 185-187, 194, 196-198 as well as the method claims 32-35, 38-40, 188 recite that the solid tumor stem cell or an enriched population of STSC expresses at least one marker selected from a group of specific markers and using such markers for enriching the STSCs.

In paper #13, Applicants argue that claims as amended recite the positive and negative markers, and the applicants were in possession of the claimed invention.

In response, as indicated in the previous Office action, the specification teaches that a combination of positive and negative markers identifying breast carcinoma stem cells, specifically the $B38.1^{+}CD44^{+}CD24^{-/low}lin^{-}$ breast tumor cell population. However, the amended product claims are set forth as a Markush group, not a combination of positive and negative markers, and the amended method claims remain set forth in an alternative form (and/or), thus, claims as written do not place any limitation on the combination. In another word, claims as written, any one of the recited markers could identify the STSC. This is not commensurate with the teaching of the specification, which states, "*while it is rare to identify* ***a single*** *marker that identifies a stem cell, it has often possible to identify* ***combinations*** *of positive and negative markers that uniquely identify stem cells and allow their substantial enrichment in other contexts*" (Specification, page 15, paragraph 49). The specification does not describe a single marker that identifies a solid tumor stem cell, thus, it fails to provide sufficient description for the full scope of the claims.

Moreover, the claims embrace any type of solid tumor stem cells, however, as indicated in the previous Office action, and evidenced by the cited art of record (Hartman et al, Schlom et al), the recited cell markers B38.1 and ESA are known to be present in breast carcinoma and tumors of epithelial origin, the specification fails to teach otherwise, therefore, the specification fails to provide sufficient description for identifying a STSC from *any* cell origin. Accordingly, the specification fails to support the full scope of the claims.

For reasons of record and those set forth above, the instant specification fails to meet the written description requirement set forth under 35 U.S.C. §112, 1st paragraph.

ENABLEMENT REQUIREMENT

Claims 32-35, 38-40, 188, and 198 stand rejected under 35 U.S.C. 112, 1st paragraph, and the rejection now applies to claims 1-14, 18-30, 185-187, 194, 196, and 197, for reasons of record and following.

In paper #13, Applicants argue that claims as amended recite the positive and negative markers, thus, the specification enables one to practice the claimed invention. Applicants further argue that the skilled in the art could also use the *in vitro* and *in vivo* assays provided in the specification to verify the tumorigeneicity of the selected STSC. Applicants cited case law to indicate, "As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims".

In response, the citation is exactly the concern of the Office. As clearly set forth in the previous Office action, the enablement rejection is a scope one, i.e. the specification is enabling for enriching STSCs for mammary and perhaps ovarian carcinoma by identifying and isolating the $B38.1^{+}$ $CD44^{+}$ $CD24^{-/low}$ lin^{-} cell population, but is not enabling for enriching *any* solid tumor stem cells because the specification fails to teach a single or one combination of universal marker(s) that recognizes all of the tumor stem cells from *any* origin.

Although the amended claims recite specific markers, the claims are set forth in alternative terms. As indicated in the paragraph 49 of the specification and cited in the Response of paper #13, the combination of markers identifies the STSC, not a single marker alone. The claims as written should stand alone to enable the claimed invention, the discussed in vivo and in vitro assays are well known in the art, they are the conventional methods for identifying the STSC, and thus not part of the invention.

The Janeway Jr. reference was cited as a showing of what is known in the art for the CD markers, they do not appear to be tumor stem cell-specific. The arguments presented in this section of the Remark are more relevant to the art rejection, thus, would be addressed in the appropriate section.

For reasons of record and those set forth above, the instant specification fails to meet the statutory enablement requirement set forth under 35 U.S.C. §112, 1st paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-8, 18, 20, 21 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Salmon et al* (New Eng J Med 1978;298:1321-7) and as evidenced by

Janeway, Jr. et al (Immunobiology, 1999) and *Hartman et al* (Int J Cancer 1999;82:256-67).

In paper #13, Applicants argue that claims as amended recite specific markers, *Salmon et al* does not disclose all of the elements as present claims. Specifically, applicants argue that Salmon does not appear to show that cells grown in the bioassay consistently form new tumors when transplanted in vivo, that Salmon does not disclose cells that express a cell surface marker selected from CD44 or epithelial specific antigen (ESA).

The amendments and arguments have been fully considered but they are not found persuasive.

Salmon et al disclose isolated solid tumor stem cells, i.e. isolated from the ovarian carcinoma, and form colonies in vitro (gave rise to new tumor cells, thus tumorigenic). While the publication is not dedicated to the *in vivo* characteristics of the tumor stem cells, *Salmon et al* clearly teach (2nd paragraph, page 1321) it has been shown previously that the tumor stem cells are responsible for population renewal and colonizing property of a metastatic neoplasm (forming new tumors when transplanted in vivo), and the colony-forming assay correlates well with the in vivo property of STSC, thus is more reliable than other measures. Although *Salmon et al* do not teach the markers of the tumor stem cells, the Office has shown that *Janeway, Jr. et al* teach the recited CD markers are expressed mostly in cells of hematopoietic lineage (Appendix I), thus, would intrinsically lack detectable levels of expression in a tumor cell that is not derived from hematopoietic lineage. Likewise, the Office has also shown that *Hartman*

et al teach that ovarian epithelial cancer cells (carcinoma) express epithelial specific antigen (1st paragraph, page 256), thus, the disclosed ovarian epithelial tumor stem cells taught by *Salmon et al* would intrinsically express ESA.

With respect to CD44, none of the rejected claims under this section requires CD44 position.

With respect to the term, "ESA", the counsel for Applicants argues in paper #13 that the term "ESA" is well known to those skilled in the art to refer to a specific antigen, not a general group of antigens that are found on epithelial cells, particularly ESA is also identified as Ep-CAM and EGP40.

In response, words of the claims are generally given their ordinary and customary meaning, unless it appears from the written description that they were used differently by the applicant. Where an applicant chooses to be his or her own lexicographer and defines terms with special meanings, he or she must set out the special definition explicitly and with "reasonable clarity, deliberateness, and precision" in the disclosure to give one of ordinary skill in the art notice of the change. See *Teleflex Inc. v. Ficosa North America Corp.*, 299 F3d 1313, 1325, 63 USPQ2d 1374, 1381 (Fed. Cir. 2002), *Rexnord Corp. v. Laitram Corp.*, 274F.3d 1336, 1342, 60 USPQ2d 1851, 1854 (Fed. Cir. 2001), and MPEP § 2111.01. Applicants are reminded when arguing that a term in the claim is limited to the special definition set forth in the written description, they should do so by referring specifically to the page and line/paragraph number of the specification. In the instant case, the specification fails to define the term, and fails to even mention Ep-CAM or EGP40. With respect to whether the term is well

known in the art, a quick search of patent and pre-grant publication database (EAST) found only one pre-grant publication 2003/0032184 (published post-filing) teaching that ESA is also known as Ep-CAM (paragraph 0037), however, there, "ESA" is known as "epithelial surface antigen (ESA)", whereas the instant claims recites, "epithelial **specific** antigen". The only U.S. patent (6,197,523) that recites "**epithelial-specific antigens**" teaches that they include EMA (as taught in ***Hartman et al***) as well as Ep-CAM". Additionally, the MPEP states that the arguments of counsel cannot take the place of evidence in the record . *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716,718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results. MPEP 716.01(c). Therefore, the *Hartman* reference remains applicable.

With respect to Janeways Jr. reference, applicants argue that Janeway, Jr. shows that certain lineage markers are found on cells of the hematopoietic lineage because his subject of interest is the immune system and cited a web site, "Immunology Link" as support that CD antigens are also found in endothelial cells.

In response, the assertion regarding the Janeway Jr. reference is baseless and in error. *Janeway Jr. et al* teach the general knowledge regarding mammalian cells expressing CD markers, whether they are hematopoietic lineage or not. The response fails to specifically point out which CD marker taught differently by *Janeway Jr.* and the cited web site. A quick comparison would find consistency in the teachings of *Janeway, Jr.* and the cited web site listing. The majority of CD lineage markers recited in the

claims are only expressed in hematopoietic cells, particularly monocytes and lymphocytes. In *Janeway, Jr.* reference, CD31 and CD140b are listed as expressed in both monocytes and endothelial cells, the same as the web listing, and the web listing shows blank for cells expressing CD140b. The web listing also teaches that CD44 is expressed in the leukocytes and erythrocytes, and does not teach that it is a stem cell mark. In fact, *Janeway, Jr.* book is the second reference textbook listed in the web site. In conclusion, the teaching of *Janeway, Jr.* illustrated what is well known in the art regarding the CD marker recited in the claims. The specification and the supporting reference cited in the arguments fail to teach otherwise. Accordingly, the citation stands in the absence of factual evidence to the contrary.

Applicants go on to argue that the examiner has not shown that the Salmon ovarian epithelial cells would intrinsically lack detectable levels of expression of CD markers or expressing ESA.

In response, the claims as written encompass any solid tumor cell that can give rise to new tumor cells (tumorigenic), including the STSC of ovarian carcinoma. The Office has shown in the form of evidence by the skill artisan that the epithelial specific antigen would be expressed in the ovarian carcinoma cells, and the CD markers would not be expressed in non-hematopoietic and non-endothelial cells, such as ovarian epithelial tumor stem cell. The analysis is consistent with the teaching of the specification, and the specification fails to teach otherwise. In the rebuttal, Applicants should provide factual evidence to show that the claimed STSC differs from the STSC taught by Salmon et al, but failed to do so. Applicants are reminded that the Office does

not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the prior art products do not necessarily or inherently possess characteristics of claimed tumor stem cells, which requires factual evidence demonstrating that actual, unobvious differences exist (or that the claimed products are functionally different than those taught by the prior art) and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPBI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922, 1923 (BPAI 1989).

Accordingly, *Salmon et al* anticipate the instant claims, and the rejection stands.

Claims 1, 3-8, 18, 20, 22 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Salmon et al* (US 4,411,990, IDS/A1).

Applicants presented similar arguments as did for the foregoing Salmon reference, which has been discussed above, will not be reiterated.

With respect to the specifics of this reference, it is noted that *Salmon et al* clearly teach tumor stem cells serve as the seeds of metastatic spread of cancer and the colony-forming, and the *transplantable* nature of these cells could be used for various studies (column 1, lines 19-36). *Salmon et al* clearly teach the isolating process and a gelable single cell suspension (column 5, lines 15-47). Therefore, *Salmon et al* clearly teach an isolated cell that is tumorigenic and that the cells grown in the bioassay form

new tumors when transplanted in vivo. The various epithelial tumor cells would intrinsically express the ESA marker as evidenced by the Hartman reference.

Accordingly, the rejection stands.

Claims 1-8, 18, 23-29, 185-187, 194, 196, and 197 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Martin et al* (Exp Hematol 1998;26:252-64), and as evidenced by *Schlom et al* (US 4,612,282), and the rejection now applies to the amended claim 198.

In paper #13, Applicants argue that Martin teaches enrichment of heterogeneous cancer cells from normal non-cancerous blood cells, not the enrichment of solid tumor stem cells. Applicants go on to argue that Martin does not disclose an isolated cell that is tumorigenic and does not appear to show the cells obtained from the blood form new tumors when transplanted in vivo, and Martin does not show an enriched population of STSCs enriched for CD44 expression.

In response, the rejected claims are not the method claims, thus, the starting materials and process for obtaining the cell are irrelevant, only the characteristics of the enriched cells are relevant.

Specifically, *Martin et al* teach isolating metastatic tumor cells from the peripheral blood. Given the plain meaning of the word, the term, "metastatic tumor" means in the context of cancer, "a secondary cancerous growth formed by transmission of cancerous cells from a primary growth located elsewhere in the body", therefore, these cells have been shown to form new tumor growth *in vivo*. The primary site of the metastatic tumor

cells taught by *Martin et al* is breast cancer, a solid tumor, thus, *Martin et al* do teach a solid tumor stem cell derived from a solid tumor and tumorigenic. The term "enrichment" is a relative term, the cells taught by *Martin et al* have been enriched at least 25-fold compared to the original collected tumor cells (abstract), wherein about 4% of the cells in the enriched population express CD44 (section in page 257), therefore, the end cell population would also be enriched for CD44. They go on to teach that such result is consistent with the previous study in animal models "SHOWING THAT ONLY A SMALL PERCENTAGE OF THE CIRCULATING TUMOR CELLS IS ABLE TO SUCCESSFULLY INITIATE METASTATIC COLONIES" (i.e. tumorigenic stem cells, last paragraph, page 262). The disclosed tumor stem cells are derived from mammary epithelial cells, would intrinsically not expressing CD2, CD3, CD10, CD14, CD16, CD31, CD45, CD64, and CD140b. While not relied upon, *Schlom et al* teach that B38.1 intensely expressed in mammary carcinoma (breast epithelial cancer, table I), possess a "pancarcinoma" pattern of binding activity (column 7, lines 2-4), and could be used for diagnosis of primary and metastatic breast tumor (column 10, line 1-51). Since the tumor stem cells taught by *Martin et al* are breast carcinoma cells, they would intrinsically express B38.1.

Applicants additionally argue, citing page 262 of Martin reference, that Martin does not teach that CD44+ cells are tumorigenic. While this is true, the cells taught by *Martin et al* meet claim limitation with regard to the characteristics of the cell population, thus, still meet claim limitation. Applicants also argue that Schlom et al do not teach that B38.1 marker could be used for selecting tumor stem cells, while this is true, the claims rejected are drawn to cells, not the method of selecting cells. Schlom et al do teach that

the B38.1 are positive in metastatic tumor cells (tumorigenic stem cells) as well as the primary cells, and strongly expressed in mammary carcinomas, meaning most of the cells in the solid tumor would stain (expressing the marker), including the STSCs, and the specification has not taught otherwise. Accordingly, in the absence of factual evidence, the breast carcinoma cells taught by Martin et al intrinsically express B38.1.

Moreover, applicants deny that the cells taught by *Martin et al* are the same type as disclosed in the specification. In response, both the specification and the Martin reference disclose breast cancer carcinoma, the art of record has shown (Schlom et al) that the marker is general for all breast carcinoma cells, primary or metastatic, not limited to a particular cell population, and breast cancer cells from different individual may have minor variations in marker expression, they share common marker expression and biological behavior in vitro and in vivo. And most importantly, the claims encompass any type of tumor stem cells that derived from any solid tumor, particularly epithelial breast cancer (amended claim 198), therefore, the claims encompass the tumor stem cells taught by *Martin et al*. Accordingly, in the absence of factual evidence to the contrary, the tumor stem cells taught by *Martin et al* meet claim limitation.

Accordingly, *Martin et al* anticipate instant claims.

Claims 1, 3-7, 9-13, and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Nierodzik et al* (Blood 1998;92:3694-3700).

In paper #13, applicants argue that *Nierodzik et al* does not disclose all the elements of the claimed invention, only discloses that thrombin can induce a metastatic

phenotype, thus, the cell is not necessarily tumorigenic. Applicants particularly argue that *Nierodzik et al* does not disclose a cell surface marker selected from CD44 or ESA.

In response, *Nierodzik et al* teach an isolated population of tumor cells derived from colon carcinoma and melanoma (solid tumors) and treatment with thrombin would *enhance* the metastasis by 10-160 fold and inducing a pulmonary metastatic phenotype (1st paragraph of the article). Without a STSC, the metastatic phenomenon could not be *enhanced,* thus, the solid tumor stem cells are necessarily present. As evidenced by *Hartman et al, and Janeway Jr. et al*, the disclosed colon epithelial tumor stem cells intrinsically express ESA, B38.1, and lack detectable levels of expression of CD2, CD3, CD10, CD14, CD16, CD31, CD64, and CD140b.

Accordingly, the rejection stands.

Claims 1, 3, 4, 6, 9-14, and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Bromberg et al* (PNAS 1995;92:8205-9).

In paper #13, applicants argue that *Bromberg et al* does not disclose all the elements of the claimed invention, only discloses that thrombin can induce a metastatic phenotype, thus, the cell is not necessarily tumorigenic. Applicants particularly argue that *Bromberg et al* does not disclose a cell surface marker selected from CD44 or ESA.

In response, *Bromberg et al* teach an isolated tumor stem cell derived from melanoma, transfected with a retroviral vector encoding a mutant extracellular TF, and the tumorigenic ability of tumor stem cells were enhanced by the TF, and the test was performed by introducing the transfected cells in SCID mice. As evidenced by Hartman

et al, and Janeway Jr. et al, the disclosed melanoma stem cells intrinsically express ESA, and lack detectable levels of expression of CD2, CD3, CD10, CD14, CD16, CD31, CD64, and CD140b.

Accordingly, *Bromberg et al* anticipate the instant claims, and the rejection stands.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23 and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Martin et al* (Exp Hematol 1998;26:252-64), in view of *Salmon et al* (US 4,411,990, IDS/A1).

The prior rejection of claims 32-40, 188, and 198 are drawn in view of the claim amendment because neither *Martin et al* nor *Salmon et al* teach using the particular markers for enriching tumor stem cells.

However, the rejection of claims drawn to the enriched STSC stands, because the cells could be enriched by other methods such as taught by *Martin et al* and *Salmon et al.*

Claims 1, 18, and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Salmon et al* (US 4,411,990, IDS/A1), in view of *Jeffries et al* (Mol Cell Bio 2000 Jun;20:3928-41).

In paper #13, applicants allege that the rejection is based on improper hindsight reasoning. Because before the applicant's disclosure in the specification, it was not known that solid tumors contain solid tumor stem cells, thus, one of skill in the art would not have been motivated to add Notch ligand to a culture of solid tumors.

The argument has been fully considered but they are not persuasive.

This is because the tumor stem cells of a solid tumor has been disclosed and identified long before the instant filing date, for example, by *Salmon et al* using different methods, which the applicants still call for using them to verifying the STSCs isolated by the instantly claimed invention (The response, 1st paragraph, page 13). In fact, the cited reference of *Salmon et al* teach culturing tumor stem cells in vitro, adding nutrients such as METGF to culture system to promote stem cell colony growth (column 4, lines 35-60).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Salmon et al,* by simply adding Notch ligand to the culture medium for culturing tumor stem cells as taught by *Jefferies et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it would enhance the yield of STSC. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

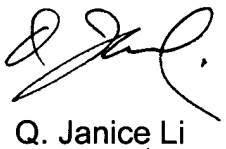
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).



Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
August 18, 2003